BEST PRACTICE

Management of stable angina

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Ischaemic heart disease may present as a wide variety of clinical entities including unstable or stable angina pectoris, acute myocardial infarction, and occasionally heart failure. Chronic stable angina is a common condition and results in a considerable burden for both the individual and society. The goals in management are (i) treatment of other conditions that may worsen angina; (ii) modification of risk factors and treatment with medications for coronary artery disease to improve outcome; and (iii) effective relief of anginal symptoms. There are limitations to the methods available to risk-stratify patients, and the optimal treatment strategy remains unclear. The benefits of lifestyle modification cannot be over-emphasised, and appropriate attention to modifiable risk factors is paramount. The mortality benefit of lipid lowering treatment and antiplatelet therapy is well proved. However the evidence base for anti-ischaemic therapy is less rigorous, being based mainly on extrapolations from studies of acute coronary syndromes. Angioplasty has been shown to be more effective in relief of symptoms than medical therapy alone, but provides no mortality benefit. Coronary artery bypass surgery, however, has been shown to reduce mortality in patients with severe proximal coronary disease when compared with medical management alone.

The goals in management of chronic stable angina are (i) treatment of other conditions that may worsen angina; (ii) modification of risk factors and treatment with medications for coronary artery disease to improve outcome; and (iii) effective relief of anginal symptoms

EPIDEMIOLOGY

The epidemiology of ischaemic heart disease is changing. The population is growing older and patients are now more frequently surviving myocardial infarction. The prevalence of risk factors such as diabetes mellitus and hypertension has also been seen to increase. As chronic stable angina may be the initial manifestation of coronary artery disease in about 50% of patients, its prevalence is also increasing, and it is possible that this condition affects 4%–5% of Western populations. This increase in both morbidity and mortality has important socioeconomic implications.

DIAGNOSIS

History

Angina is a clinical diagnosis that may be established by obtaining a careful history. Typical angina presents as chest tightness or heaviness brought on by exertion and relieved by rest. The discomfort is frequently felt in the left arm and jaw also. More atypical presentations such as epigastric or hypochondrial pain occur rarely. The discomfort may be exacerbated by cold weather, heavy meals, or states of high emotion.

The Canadian Cardiovascular Society has produced guidelines relating to the grading of severity of angina (see box 1).

Examination

Clinical examination of patients with stable angina is often normal. However during episodes of chest pain features associated with autonomic nervous system over-activity or left ventricular dysfunction may be present. Clinical examination should also include assessment of conditions known to be associated with ischaemic heart disease, for example, xanthelasma, hypertension, or peripheral vascular disease. Conditions known to exacerbate pre-existing coronary artery disease, for example, hyperthyroidism, anaemia, or aortic stenosis should also be sought.

INVESTIGATION AND RISK ASSESSMENT

Successful management of the patient with chronic stable angina requires correct stratification by assessing the risk of future coronary events. Patients at low risk for such events have a relatively good prognosis; revascularisation procedures (balloon angioplasty or surgery) offer no benefit over medical management. Such patients should be offered medical treatment as their first option.

Non-invasive

Electrocardiography

A rest 12 lead electrocardiogram (ECG) should be recorded in all patients with symptoms suggestive of angina pectoris, however this may be normal in approximately 50% of patients with chronic stable angina.¹ Normal appearances of a 12 lead ECG do not exclude severe coronary artery disease. Evidence of left ventricular hypertrophy or ischaemic ST-T segment changes increase the probability of underlying coronary artery disease; the presence of Q waves suggestive of previous

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Box 1: Canadian Cardiac Society classification of angina

- Class I: ordinary physical activity does not cause angina.
- Class II: angina causes slight limitation of day to day activity.
- Class III: symptoms cause marked limitation of ordinary activity.
- Class IV: symptoms occur when undertaking any physical activity or at rest.

Box 2: Absolute contraindications to exercise ECG testing

- Acute myocardial infarction within the last two days.
- Severe or symptomatic aortic stenosis.
- Symptomatic heart failure.
- Acute pulmonary embolism.
- Acute myocarditis or pericarditis.
- Acute aortic dissection.
- Resting blood pressure >200/120 mm Hg.
- Acute systemic illness.

myocardial infarction makes coronary artery disease very likely.² The presence of arrhythmia on a rest ECG does make the presence of coronary artery disease more likely, however other underlying causes must also be sought.

An ECG obtained during an episode of chest pain will be abnormal in 50% of patients with angina who have a normal rest ECG. Dynamic ST-T segment changes with chest pain are highly suggestive of coronary artery disease, and carry a worse prognosis. If these changes are unequivocal and at low workloads these patients may require no further non-invasive testing. "Pseudonormalisation" of the ECG in patients with abnormal ST-T segments at rest may occur during episodes of chest pain. This too is a sign of underlying coronary artery disease.

Chest radiography

The chest radiograph is often normal in patients with coronary artery disease, and its usefulness in routine investigation of these patients is not well established. It is more likely to be abnormal in patients with previous or acute myocardial infarction, and non-cardiac causes of chest pain. Chest radiography may also reveal complications of coronary artery disease such as pulmonary oedema in congestive heart failure.

Stress testing**(1) Exercise ECG**

By far the most available form of stress testing is the exercise ECG. First described in 1932, this procedure has been in widespread clinical use for many decades.³ Exercise ECG testing is safe, however both myocardial infarction and death occur at a rate of approximately 1/2500 tests. The absolute contraindications to exercise testing are shown in box 2.

Other contraindications are relative and include left main coronary artery disease, moderate aortic stenosis, hypertrophic obstructive cardiomyopathy or other outflow tract obstruction, and high degree atrioventricular block.

Some studies have shown exercise ECG testing to be less specific and sensitive in women than men.^{4,5}

(2) Stress imaging

Both nuclear and echocardiographic imaging modalities can be utilised in the diagnostic and prognostic assessment in patients with suspected coronary artery disease in whom an exercise ECG is likely to be unreliable. A variety of techniques can be employed to introduce stress and these include

exercise, vasodilators (for example, adenosine), and inotropes (for example, dobutamine). Not only do they provide additional information for risk stratification but also functional information in coronary artery disease.⁶⁻⁸

Newer technologies

Both electrobeam computed tomography and magnetic resonance angiography provide information regarding the severity of coronary artery disease.⁹ However neither of these techniques is currently widely available and hence their precise role in risk assessment of patients with coronary artery disease will not be discussed here.

Invasive investigations**Coronary angiography**

Coronary angiography remains the most accurate method for the diagnosis of clinically important obstructive coronary artery atherosclerosis.¹⁰ The technique involves the insertion of a catheter into the heart via a peripheral artery. Left heart catheterisation is usually performed via the right femoral artery and involves selective cannulation of the left and right coronary arteries, and ventriculography.

Minor complications occur in approximately 5% of patients. Such complications include localised bruising around the arteriotomy, allergy to contrast agents, and vasovagal reaction. Major complications, for example, death, myocardial infarction and stroke, are rare affecting approximately 0.25% of patients. Major complications are more common in those with advanced cardiac disease.¹¹

MANAGEMENT

This involves alteration of lifestyle, treatment of precipitating factors, drug treatment, and possibly percutaneous intervention or surgery if medical treatment fails.

Lifestyle management

Although the mainstay of treatment of angina is pharmacological, the importance of lifestyle adjustments must not be underestimated. Of these, smoking cessation, dietary control, and increased exercise are the most important.

Smoking cessation

The causal link between smoking and premature coronary artery disease is well demonstrated.¹² Smoking cessation is probably the single most important intervention for primary and secondary prevention of coronary artery disease and yet is the most difficult to address successfully.¹³ The physician must highlight the importance of smoking cessation to all smoking patients while accepting that smoking is a chronic problem requiring long term multidisciplinary management.¹⁴ Advice should be given to assist smokers to stop, and pharmacological assistance considered with either nicotine replacement therapy or bupropion¹⁵ when not contraindicated.

Weight loss, exercise, and diet

The incidence of angina is directly associated with increasing body mass.¹⁶ Patients with a body mass index of more than 25 should be encouraged to lose weight by diet control and increased exercise.¹⁷ Reduction in weight will help control of hypertension.¹⁸

The incidence of coronary artery disease is higher in patients with a sedentary lifestyle.¹⁹ All patients should be encouraged to increase their levels of aerobic exercise such as brisk walking, cycling, or swimming.²⁰ Where compliance or motivation is low, patients should be encouraged to incorporate aerobic exercise into their daily routine, for example walking or cycling to work.

All newly diagnosed patients with angina should be given dietary advice, and where possible, assessed by a dietitian.^{16,17} The overall intake of fat should be reduced, especially

saturated fats found mostly in meat and dairy products. Consumption of oily fish two to three times a week may help to reduce the level of triglycerides due to the high omega-3 content.²¹ Patients eating a diet with high proportions of fruit and vegetables per day are less likely to develop coronary artery disease.²² Although the mechanism is as yet unclear it is thought to be because of the antioxidants, vitamins, and folic acid. However, the Heart Protection Study shows that taking vitamin tablets does not have the same effect.²³

DISEASES ASSOCIATED WITH DEVELOPMENT OF ANGINA

Hypertension, diabetes, and hyperlipidaemia are associated with accelerated development of atherosclerosis. When identified, prompt treatment is indicated.

Hypertension causes arterial wall stress, vascular turbulence, and endothelial damage leading to increased plaque formation.²⁴ Effective treatment of hypertension reduces the relative risk of myocardial infarction by 20% and stroke by 40%.²⁵ Hypertension should be identified on three separate readings one week apart before treatment. Current guidelines for the management of hypertension are summarised elsewhere.²⁶

Diabetic patients develop ischaemic heart disease earlier than non-diabetic patients due to accelerated atherosclerosis secondary to glycolysation of endothelial components.^{27, 28} Poor blood glucose control is associated with early atheroma formation and increased plaque burden.²⁹ Routine management of diabetic patients should assess other risk factors for atherosclerosis development such as smoking, hypertension, and hyperlipidaemia.³⁰

Patients with diagnosed hyperlipidaemia should be given appropriate advice regarding diet, weight loss, and regular aerobic exercise. However adequate control of hyperlipidaemia usually requires the concurrent use of lipid lowering drugs.³¹

PHARMACOLOGICAL MANAGEMENT OF ANGINA

The drugs used to manage angina can be split into those that reduce mortality and those shown only to control symptoms.

(1) Antiplatelet agents: aspirin and thienopyridine derivatives

Several studies have shown the benefits of aspirin in acute coronary syndromes and unless otherwise contraindicated aspirin should be prescribed in all patients with acute coronary syndromes.³² Aspirin has been demonstrated to reduce death from cardiac causes and non-fatal myocardial infarcts by almost half.³³ These benefits have also been demonstrated in other arteriosclerotic disease.³³ The mechanism of action of aspirin is as an anti-inflammatory and antiplatelet agent; it causes irreversible acetylation of platelet cyclo-oxygenase inhibiting the production of thromboxane A₂, and thus platelet aggregation.

The beneficial effect of aspirin has been proved over a dose range of 75 mg to 325 mg. Given the potential for increased gastrointestinal side effects at higher doses it is recommended that patients be given an initial loading dose of 300 mg followed by maintenance of 75 mg once daily for an indefinite period.³⁴

The thienopyridine derivatives, ticlopidine and clopidogrel act by blocking adenosine diphosphate mediated platelet aggregation and by preventing the formation of high affinity platelet fibrinogen receptors.^{35, 36} Ticlopidine use has been limited by occurrences of severe neutropenia in 2%–3% of patients, an effect reversed on discontinuation of the drug. The CAPRIE study showed that clopidogrel was slightly more effective than aspirin in reducing ischaemic complications (ischaemic stroke, myocardial infarction, or vascular death) in patients with atherosclerotic vascular disease.³⁶ Therefore clopidogrel is indicated in those with aspirin intolerance. The

CURE study randomised 12 562 patients with non-ST elevation acute coronary syndromes to clopidogrel or placebo for 3–12 months.³⁷ The trial demonstrated that the addition of clopidogrel to conventional treatment with aspirin results in a 23% reduction in myocardial infarction at nine months. There was no significant reduction in death or stroke. The combination of aspirin and clopidogrel has not been investigated in stable angina. The effects of very long term clopidogrel use are as yet unreported.

(2) β -Adrenoreceptor antagonists

The mechanism of action of β -adrenoreceptor antagonists is to decrease myocardial oxygen demand through a reduction in heart rate, cardiac after-load, and myocardial contractility.³⁸ Although β -adrenoreceptor antagonists do not offer survival benefit in isolated stable angina, risk reduction benefits have been demonstrated in hypertension¹⁶ and acute myocardial infarction,^{39, 40} and hence unless otherwise contraindicated, β -adrenoreceptor antagonists are considered as first line agents. β -Adrenoreceptor antagonists reduce the risk of subsequent myocardial infarction.⁴¹

(3) HMG-Co-A reductase inhibitors

Several trials have demonstrated that patients with arteriovascular disease and hyperlipidaemia benefit from therapy with HMG-Co-A reductase inhibitors ("statins").^{31, 42, 43} In the Scandinavian Simvastatin Survival Study (4S) 4444 patients with a history of angina or acute myocardial infarction and raised fasting cholesterol between 5.5–8.0 mmol/l were randomised to receive simvastatin or placebo.³¹ The study showed total mortality and cardiovascular mortality were decreased significantly in the treated group. Similar results were obtained from the CARE trial⁴² and LIPID trial.⁴³ More recently, the Heart Protection Study group demonstrated those patients at increased risk of coronary artery disease with normal cholesterol levels had a one third reduction of myocardial infarction, stroke, or revascularisation.⁴⁴ This may suggest a novel mechanism of action.

Patients deemed to be at high risk of ischaemic heart disease (for example, family history, hypertension, diabetes) should have lipid levels rechecked three months after dietary changes and if total cholesterol remains >5.0 mmol/l or low density lipoprotein cholesterol >3.0 mmol/l then a statin should be prescribed.^{45–48} The use of statins in low risk patients remains controversial with potential health economy implications.⁴⁹

(4) Angiotensin converting enzyme inhibitors

Angiotensin converting enzyme (ACE) inhibitors interrupt the rennin-angiotensin-aldosterone axis by preventing the conversion of angiotensin I to angiotensin II. They also increase plasma levels of bradykinin, which possesses vasodilatory and tissue protective properties. The role of ACE inhibitors in hypertension⁵⁰ and left ventricular dysfunction is widely accepted.^{51, 52}

The use of ACE in patients with vascular disease who do not have the traditional indications for ACE inhibition increased following the Heart Outcomes Prevention Evaluation (HOPE) study in which 9541 normotensive patients were randomised to ramipril or placebo over a six year period.⁵³ The HOPE study demonstrated a significant reduction in mortality in patients with a high risk for cardiovascular events due to a history of previous ischaemic heart disease, stroke, peripheral arterial disease or in individuals with diabetes. ACE inhibitors are thought to reverse endothelial dysfunction.

(5) Calcium channel antagonists

Calcium channel antagonists are divided into two groups: dihydropyridines such as nifedipine, and non-dihydropyridines such as diltiazem and verapamil. The

mechanism of action of both type of calcium channel antagonists is to prevent the entry of extracellular calcium through the myocardial membrane thus reducing myocardial oxygen demand, arterial pressure, and contractility.³⁸ Although widely prescribed for symptomatic control of angina, calcium channel antagonists shows no mortality benefit in angina.^{40–54} Short acting dihydropyridines may increase anginal symptoms by inducing reflex tachycardia and should be prescribed with a β -adrenoreceptor antagonist.⁵⁵ Patients intolerant of β -adrenoreceptor antagonists should receive a non-dihydropyridine calcium channel antagonist.

(6) Nitrates

Nitrates are vasodilators, reducing cardiac preload and after load, and hence decreasing myocardial oxygen demand.⁵⁶ Short acting sublingual nitrates are used in the immediate relief of angina whereas long acting oral preparations are used as prophylaxis of symptoms.⁵⁷ Intravenous preparation can be used in the symptomatic management of unstable angina. Prolonged use of nitrates leads to tolerance and a requirement for dose increases that may be limited by hypotension.⁵⁸ The effect of tolerance can be reduced by a nitrate free period of eight hours. As with other symptomatic treatments, nitrates demonstrate significant symptomatic relief in angina but no reduction in overall mortality.

(7) Potassium channel activators

The only potassium channel activator currently licensed is nicorandil. Activation of potassium channels causes vasodilation and also has nitrate-like venodilatory properties without the disadvantage of tolerance.⁵⁹ The IONA study showed significant improvement in outcome due to a reduction in major coronary events by therapy with 20 mg nicorandil twice daily in addition to standard antianginal therapy.⁶⁰ The mechanism is postulated to be due to ischaemic preconditioning of the myocardium.

REVASCULARISATION FOR CHRONIC STABLE ANGINA

Percutaneous coronary interventions

There are currently two routinely available modalities for revascularisation in patients with coronary artery disease, percutaneous coronary interventions (PCI) such as balloon angioplasty and stent implantation, and coronary artery bypass grafting (CABG) surgery. The benefits of these treatments can only be shown in long term follow up studies, and although these exist, the treatments have usually improved during this interval, and thus it may not always be accurate to extrapolate these results to current practice.

The advantages of PCI for the treatment of coronary artery disease are many and include a low level of procedure related mortality, a short hospital stay, and an early return to activity. Significant disadvantages include the fact that all patients are not suitable for these interventions, a significant risk of restenosis, and a risk of acute coronary occlusion during percutaneous transluminal angioplasty, although this last complication has lessened in frequency since the more routine use of intracoronary stents.⁶¹

Percutaneous intervention v medical treatment

RITA-2 randomised patients with coronary artery disease and angina to medical treatment or PCI.⁶² Follow up of these patients showed that those treated with PCI had less angina at both three months and two years, but no difference in death or myocardial infarction. This finding has also been confirmed in meta-analysis.⁶³

The use of PCI to treat patients with chronic stable angina and characteristics that define high risk of mortality has not been tested.

Information for patients and doctors

- The British Heart Foundation leaflet *Angina* has extensive information and advice for patients with this condition.
- The British Heart Foundation website www.bhf.org.uk has extensive information for patients and practitioners, as well as links to other sites of interest.
- Information for patients and contact details of self help groups can also be found on the NHS Direct website at www.nhsdirect.nhs.uk.
- The British Cardiac Society website at www.bcs.com has guidelines for the management of angina, as do both the American College of Cardiology at www.acc.org/ and the European Cardiac Society at www.esc.be/.

Coronary artery bypass grafting v medical treatment

Randomised controlled trials up to the mid-1980s showed that in comparison with medical treatment, CABG carried an increase in mortality in the first 12 months after surgery, but thereafter appeared to reduce the risk of death from coronary artery disease in patients followed up at five and 10 years. Greatest benefit in terms of survival occurred in patients with more severe disease, for example, left main coronary artery stenosis, multivessel disease with left ventricular dysfunction, or previous myocardial infarction.^{64–65} These findings have been confirmed by meta-analysis.⁶⁶

Percutaneous intervention v coronary artery bypass grafting

Both the BARI⁶⁷ and EAST⁶⁸ trials looked at PCI compared with CABG for the treatment of patients with coronary artery disease. The populations studied were widely mixed and consisted of patients with both stable and unstable angina, however these large studies represent the best comparative data available. The results of both of these trials at five year follow up have shown that early and late survival rates have been equivalent for the PCI and CABG groups. The BARI trial showed that the subgroup of patients with diabetes had a significantly better survival with CABG. In both trials the PCI group had significantly higher rates of reintervention at late follow up.

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